## REMARKS

Applicants have amended Claim 1, to recited "An isolated antibody...." Applicants submit that no new matter was added by the amendments, and that support for the amendments can be found throughout the specification. Support for the amendment to Claim 1 can be found, for example, in ¶ [0246] of the specification.

Applicants thank the Examiner for the review of the instant application. Applicants request that the Examiner confirm that the objection to the specification was withdrawn in response to Applicants' amendment of the specification. In addition, Applicants note that the Examiner has neither expressly maintained nor withdrawn the rejection of Claims 1-5 under 35 U.S.C. § 102(b) as anticipated by Baker, or the rejection of Claims 1, 2, 4 and 5 under 35 U.S.C. § 103(a) as unpatentable over TrEMBL accession no. Q9Y332 in view of Sibson and/or Brandon. Applicants request that the Examiner confirm for the record that these rejections are withdrawn.

Claims 1-5 are presented for examination. The rejections to the presently pending claims are respectfully traversed.

**Correction of Inventorship under 37 CFR §1.48(b)**

On page 6 of the previous Amendment and Response (mailed December 7, 2004), Applicants requested that several inventors listed on page 5 of the previous Amendment and Response be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. Applicants respectfully submit that this statement satisfies the requirement of 37 C.F.R. 1.48(b)(1), and note that the processing fee of $130 required under 37 C.F.R. 1.48(b)(2) was submitted with the previous response. Applicants acknowledge that Examiner has indicated that the inventorship has been changed. However, Applicants have not received a corrected filing receipt. Therefore Applicants request that the Examiner confirm that the inventors listed previously were deleted as requested.

**Priority Determination**

The PTO has previously stated that because the claimed antibody has no utility, the priority under 35 U.S.C. § 120 is set at the instant filing date, May 1, 2002. Applicants maintain that for the reasons stated below, the claimed antibodies have a credible, substantial, and specific

utility. The sequences of SEQ ID NOs: 9 and 10 were first disclosed in US Provisional Application 60/088030 filed 6/4/1998. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed antibodies, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. Therefore, Applicants submit that they are entitled to a priority date of at least August 24, 2000.

**Rejection under 35 U.S.C. §101 – Utility**

The PTO has maintained its rejection of the pending claims under 35 U.S.C. § 101 as lacking either a specific or substantial asserted utility or a well established utility. The PTO states that the present utility rejection is based upon Applicants' failure to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. The PTO asserts that it has "cited countervailing evidence [Allman *et al.*, Blood, 87(12):5257-68 (1996)] to show that the skilled artisan would have a legitimate basis to doubt the utility of the PRO874 polypeptide because the skilled artisan recognizes that protein levels are not always consistent with mRNA levels." Office Action at 3 (emphasis added). The PTO argues that this evidence provides a reason for one skilled in the art to question the objective truth of the statement of diagnostic or therapeutic use of the claimed antibodies. The PTO concludes that "[i]n the absence of any information on the role, activity, or expression of the PRO874 polypeptide in cancer, the examiner therefore considers these asserted utilities to not be specific and substantial because the skilled artisan would not know if PRO874 polypeptide expression could, would or should be upregulated, down-regulated, or unchanged in cancer." Office Action at 3.

Applicants respectfully disagree.

*Utility – Legal Standard*

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "to violate § 101 the claimed device must be totally incapable of achieving a useful result." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 U.S.P.Q.2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that "to overcome the presumption of truth that an assertion of utility by the applicant enjoys" the PTO must establish that it is "more likely than not that one of ordinary skill in the art would doubt

(i.e., 'question') the truth of the statement of utility." M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained [] because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art**. M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added).

*Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient*

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 U.S.P.Q. 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 U.S.P.Q. 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 U.S.P.Q. 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 U.S.P.Q. 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove

that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> *[I]n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is "an invariable exact correlation" between gene expression and protein expression. Instead, Applicants' position detailed below is that a measured change in gene expression in cancer cells establishes a "significant probability" that the expression of the encoded polypeptide in cancer will also be changed based on "a reasonable correlation therebetween."

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

**Substantial Utility**

*Summary of Applicants' Arguments and the PTO's Response*

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed antibodies have utility as diagnostic tools for cancer, particularly lung cancer. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO874 polypeptide is expressed at least two-fold higher in normal lung tissue compared to lung tumor;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, e.g. a decrease, generally leads to a corresponding change in the level of the encoded protein, e.g. a decrease;

3. Given Applicants' evidence that the level of mRNA for the PRO874 polypeptide is decreased in lung tumors compared to normal lung tissue, it is likely that the PRO874 polypeptide is decreased in lung tumors compared to normal lung tissue. Antibodies to polypeptides such as PRO874 which are differentially expressed in certain cancers are useful as diagnostic tools, alone or in combination with other diagnostic tools.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO asserts that Allman *et al.* is sufficient to establish that the skilled artisan would have a legitimate basis to question the relative expression of the PRO874 polypeptide in tumors, and the skilled artisan would not know if PRO874 polypeptide expression could, would or should be upregulated, down-regulated, or unchanged in cancer;

2. The PTO states that the present specification does not provide any testing regarding the level of expression, activity, or role in cancer of the PRO874 polypeptide;

3. The PTO argues that one skilled in the art would be required to carry out further research to identify or reasonably confirm a "real world" context of use, and therefore the invention lacks a substantial utility.

As detailed below, Applicants submit that the PTO has failed to demonstrate that this is one of the "rare cases" where the applicants have "asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." M.P.E.P. § 2107.02 III B. First, the PTO has failed to offer any evidence to support its rejection of the data in Example 18 and the Declaration of Chris Grimaldi in support of these data. Second, Applicants submit that Allman *et al.* is not contrary to Applicants' arguments, and therefore offers little evidence to support the PTO's position. Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable

correlation between the evidence and the asserted utility. **The standard is not absolute certainty**.

*Applicants have established that the Gene Encoding the PRO874 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue*

Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish that the PRO874 gene is differentially expressed in lung tumors compared to normal lung tissue, and is therefore useful as a diagnostic tool for cancer, specifically lung cancer. The PTO has acknowledged this utility for a limited number of nucleic acid probes, but maintains that it does not provide utility for the claimed antibodies. Office Action dated 9/8/2004 at 4.

Applicants previously submitted a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue. In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or under-expressed in tumor cells compared to corresponding normal tissue. Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor." First Grimalidi declaration at ¶7.

The PTO has stated that the Grimaldi Declaration is insufficient to overcome the rejection of Claims 1-5, offering two arguments. The PTO argues that:

> All polynucleotides/polypeptides from a particular tumor sample can invariably be classified as either more highly expressed, less expressed, or unchanged expression as compared to some standard level of expression. It can then be asserted that any protein/polynucleotide that is expressed in this manner can be used to detect or characterize the tumor. Such utilities are analogous to the assertion that a particular protein can be employed as a molecular weight marker, which is neither a specific or substantial utility. Office Action at 4-5 (emphasis added).

Applicants submit that this mischaracterizes Applicants' asserted utility for the claimed antibodies. Applicants have not asserted that a polynucleotide and corresponding polypeptide whose expression is unchanged can be used to detect tumors. Instead, Applicants have asserted

that polynucleotides/polypeptides whose expression is increased or decreased in tumors compared to the corresponding normal tissue are useful as diagnostic tools for cancer. The first Grimaldi declaration makes this clear: "[t]he precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue.... If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor." Paragraph 7 (emphasis added). This is not the same as an asserted utility of using a protein as a molecular weight marker since not all genes are differentially expressed in tumors. In addition, as detailed below, this is a specific utility since the PRO874 gene and protein are differentially expressed in a specific type of tumor, namely lung tumors. Thus, the PTO's rejection of the first Grimaldi declaration is based on a mischaracterization of Applicants' assertion of utility and enablement.

In rejecting the first Grimaldi declaration, the PTO also states that "no information is provided in the differential tissue expression distribution data regarding the level of expression, activity, or role in cancer of the PRO874 polypeptide." Office Action at 5. Based on Allman *et al.*, the PTO argues that "[t]he skilled artisan would not know if PRO874 polypeptide expression could, would or should be upregulated, down-regulated, or unchanged in cancer." Office Action at 5. Therefore, the PTO concludes that based on the present disclosure, one skilled in the art would be required to carry out further research to identify or reasonably confirm a "real world" context of use.

Applicants remind that PTO that the evidence of the asserted utility can be indirect evidence which is reasonably correlated to the asserted utility. As discussed below, Applicants believe that they have established for the record that it is more likely than not that one of skill in the art would accept that changes in mRNA lead to corresponding changes in the encoded polypeptide. In light of all the evidence, one skilled in the art would find it more likely than not that the PRO874 polypeptide is underexpressed in lung tumors based on the fact that the PRO874 mRNA is underexpressed in lung tumors. Thus, contrary to the PTO's assertion, Applicants have provided information regarding the expression of the PRO874 polypeptide, in the form of reasonably correlated indirect evidence. For the reasons discussed below, further research to confirm a "real world" use for the claimed antibodies is not required.

*Applicants have established that the Accepted Understanding in the Art is that there is a Reasonable Correlation between Changes in mRNA Levels and the Level of Expression of the Encoded Protein*

Applicants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO874 polypeptide in lung tumors, it is likely that the PRO874 polypeptide is also differentially expressed; and therefore the claimed antibodies are useful as a diagnostic tool for cancer, specifically lung cancer.

In response to Applicants' assertion, the PTO relies on a single reference, Allman *et al.* (Blood, 87(12):5257-68 (1996)), for the conclusion that "protein levels are not always consistent with mRNA levels." Office Action at 3 (emphasis added).

As stated previously, Applicants acknowledge that there is no *necessary* correlation between gene expression levels and protein expression levels, but a *necessary* correlation is not required to establish an asserted utility. Instead, there need only be a reasonable correlation. Therefore the fact that protein levels are not always consistent with mRNA levels does not refute Applicants' asserted utility.

In addition, the Allman reference actually supports Applicants' assertion that there is a reasonable correlation between changes in the level of an mRNA and the level of the encoded protein. In the discussion of their finding that mRNA and DNA levels were not correlated, Allman *et al.* state that "an *unanticipated* finding was that the higher BCL-6 protein levels...could not be fully accounted for by increased mRNA expression." Allman *et al.* at 5267, column 1, carryover paragraph (emphasis added). This indicates that generally, protein expression is correlated to mRNA levels, and their findings to the contrary were unexpected for that reason.

Even if the results in Allman supported the PTO's argument, which they do not as discussed above, one contrary example does not establish that one of skill in the art would believe that there is no correlation between changes in mRNA level and changes in protein level, especially in light of the more likely than not standard. As shown by the declarations, references, and textbooks discussed below, Applicants submit the working hypothesis among those skilled in

the art is that there is a positive correlation between changes in mRNA levels and changes in protein levels for a particular gene.

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also previously submitted a copy of the declaration of Paul Polakis, Ph.D., an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (submitted herewith as Exhibit 1) and (4th ed. 2002) (submitted herewith as Exhibit 2)). Figure 9-2 of Exhibit 1 shows the steps at which eukaryotic gene expression can

be controlled. The first step depicted is transcriptional control. Exhibit 1 provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Exhibit 1 at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Exhibit 1 at 453 (emphasis added). Thus, as established in Exhibit 1, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Exhibit 2, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – most obviously by controlling the production of its mRNA." Exhibit 2 at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Exhibit 2 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Exhibit 2 at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Exhibit 2 at 379 (emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (submitted herewith as Exhibit 3) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, submitted herewith as Exhibit 4. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" Exhibit 4 at 4. Of the samples tested, 81 out of 87

showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Exhibit 4 at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." Exhibit 4 at 7.

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), submitted herewith as Exhibit 5, states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein. This is sufficient rebuttal evidence to the PTO's single example to the contrary, especially in light of the comments by the authors in Allman that a lack of correlation was "unanticipated." Considering the all of the evidence, Applicants have established that it is more likely than not that one of skill in the art would believe Applicants' asserted utility.

In response to the second Grimaldi Declaration and the Polakis Declaration, the PTO argues that "[t]he examiner has cited countervailing evidence to show that the skilled artisan would have a legitimate basis to doubt the utility of the PRO874 polypeptide. The skilled artisan would not know if PRO874 polypeptide expression could, would or should be upregulated, down-regulated, or unchanged in cancer." Office Action at 7 and 9. The PTO states that Allman provides evidence that Applicants' assertion regarding a correlation between changes in mRNA level and changes in the level of the encoded polypeptide "is not absolutely true and that the skilled artisan would have a legitimate basis to doubt the utility of the PRO874 polypeptide based

solely on the disclosure regarding DNA40621-1440 in Example 18." Office Action at 9 (emphasis added). Finally the PTO argues that "in the present case the specification does not provide any testing of the level of expression, activity, or role in cancer of the PRO874 polypeptide." Office Action at 7-8, 9 and 10.

For the reasons stated above, Applicants submit that Allman is not sufficient to meet the PTO's burden of establishing a reasonable basis for one skilled in the art to doubt Applicants' asserted utility, and even if it is, Applicants have provided sufficient rebuttal evidence. The fact that the correlation between changes in mRNA and protein is not "absolutely true" is not relevant, since the correlation only needs to be a reasonable one that is more likely than not. Given Applicant's overwhelming evidence of a reasonable correlation between changes in mRNA level and changes in the corresponding protein level, Applicants submit that one skilled in the art would know that PRO874 polypeptide expression could, would and should be down-regulated in lung cancer.

Applicants also submit that a lack of known role for PRO874 in cancer does not prevent its use as a diagnostic tool for cancer. The fact that there is no known translocation or mutation of PRO874, for example, is irrelevant to whether its differential expression can be used to assist in diagnosis of cancer – one does not need to know why PRO874 is differentially expressed, or what the consequences of the differential expression are, in order to exploit the differential expression to distinguish tumor from normal tissue.

In fact the Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially expressed in cancer have utility. The caveat in Example 12 states that the utility requirement is satisfied where a protein is expressed on melanoma cells but not on normal skin, and that antibodies against the protein can be used to diagnose cancer. The position of the PTO requiring a known role for PRO874 in cancer for utility is also inconsistent with the analogous standard for therapeutic utility of a compound where "the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an 'immediate benefit to the public' and thus satisfies the utility requirement." M.P.E.P. §2701.01 (emphasis original). Here, the mere identification of altered expression in tumors is relevant to diagnosis of tumors, and, therefore, provides an immediate benefit to the public.

In addition, while Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO has

issued several patents claiming differentially expressed polypeptides and antibodies to the same, or methods employing such antibodies. (*See, e.g.,* U.S. Patent No. 6,414,117, U.S. Patent No. 6,124,433, U.S. Patent No. 6,156,500, and U.S. Patent No. 6,562,343 attached hereto as Exhibits 6-9.)

Therefore, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO874 mRNA is differentially expressed in lung tumors compared to normal lung tissue, the PRO874 polypeptide will also be differentially expressed in lung tumors compared to normal lung tissue. This differential expression of the PRO874 polypeptide makes the claimed antibodies useful as a diagnostic tool for cancer, particularly lung cancer.

*The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"*

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 U.S.P.Q. 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove

that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

Applicants remind the PTO that the M.P.E.P. cautions that rejections for lack of utility are rarely sustained by federal courts, and that generally speaking, a utility rejection was sustained because the applicant asserted a utility "that could **only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art.**" M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added). Rather than being wholly inconsistent with contemporary knowledge in the art, Applicants' asserted utility is squarely within the teaching of leading textbooks in the field, and is supported by references and the declarations of skilled experts.

The PTO has not offered sufficient arguments or references to establish "that one of ordinary skill in the art would reasonably doubt" that claimed antibodies can be used as a diagnostic tool for cancer. While Allman *et al.* offers some limited support for the PTO's position, any support for the PTO is offset by the authors' statements characterizing the results as "unanticipated" which support Applicants' position. Given the lack of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is credible and sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to overcome the PTO's evidence. The PTO has failed to provide any reasoned examination of Applicants' rebuttal evidence, instead relying on conclusory statements that the PTO has submitted "countervailing evidence." When all the evidence of record is considered, Applicants submit that they have establish that one of skill in the art would more likely than not believe that the claimed antibodies can be used as diagnostic tools for cancer, particularly lung cancer.

**Specific Utility**

*The Asserted Substantial Utilities are Specific to the Claimed Antibodies*

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed antibodies related to PRO874. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO874 gene and polypeptide in lung tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed antibodies.

As discussed above, there are significant data which show that the gene for the PRO874 polypeptide is expressed at least two-fold higher in normal lung tissue compared to lung tumors. These data are strong evidence that the PRO874 gene and polypeptide are associated with lung tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO874 gene and polypeptide with a specific disease. The asserted utility for the claimed antibodies as diagnostic tools for cancer, particularly lung tumors, is a specific utility – it is not a general utility that would apply to the broad class of antibodies.

**Conclusion**

The PTO has asserted three arguments to support its conclusion that the claimed antibodies lack a patentable asserted utility. First, the PTO asserts that Allman *et al.* is sufficient to establish that the skilled artisan would have a legitimate basis to question the relative expression of the PRO874 polypeptide in tumors, and the skilled artisan would not know if PRO874 polypeptide expression could, would or should be upregulated, down-regulated, or unchanged in cancer. Second, the PTO states that the present specification does not provide any testing or information regarding the level of expression, activity, or role in cancer of the PRO874 polypeptide. Third, the PTO argues that one skilled in the art would be required to carry out further research to identify or reasonably confirm a "real world" context of use, and therefore the invention lacks a substantial utility. Applicants have addressed each of these arguments in turn.

First, the Applicants provided a first Declaration of Chris Grimaldi stating that the gene expression data in Example 18 are real and significant. This declaration also indicates that given the relative difference of at least two-fold in expression levels, the disclosed nucleic acids and corresponding polypeptides and antibodies have utility as cancer diagnostic tools.

Second, Applicants have shown that the second Grimaldi Declaration and Polakis Declaration, the accompanying references, as well as the excerpts and references cited above, demonstrate that there is a reasonable correlation between changes in mRNA levels and a

corresponding change in protein levels. The PTO has not offered any substantial reason or evidence to question Applicants' declarations and supporting references.

Third, Applicants have shown that it is not necessary to know what role PRO874 plays in cancer to use it as a diagnostic tool. The PTO's own guidelines recognize this fact, and numerous patents have issued which claim differentially expressed polypeptides and antibodies to the same, or methods employing such antibodies.

Finally, the PTO asserts that there is no asserted specific utility. Applicants have pointed out that the substantial utilities described above are specific to the claimed antibodies because the PRO874 gene and polypeptide are differentially expressed in certain cancer cells compared to the corresponding normal cells. This is not a general utility that would apply to the broad class of antibodies.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed antibodies as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing **some** beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely... A commercially successful product is not required... Nor is it essential that the invention accomplish all its intended functions... or operate under all conditions... partial success being sufficient to demonstrate patentable utility... In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed antibodies relating to PRO874 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

**Rejections under 35 U.S.C. § 112, first paragraph – Enablement**

The PTO has also maintained its rejection of Claims 1-5 as failing to comply with the enablement requirement. Specifically, the PTO asserts that because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art clearly would not know how to use the claimed invention.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies. Applicants therefore request that the PTO reconsider and withdraw the enablement rejection of Claims 1-5.

**Rejections under 35 U.S.C. § 112, first paragraph – Written Description, New Matter**

The PTO has rejected Claims 1-5 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The PTO argues that there is no written support for the limitation "amino acids 34-321 of SEQ ID NO: 10."

As amended, the Claim 1 recites "An isolated antibody that specifically binds to the polypeptide having the amino acid sequence of amino acids 34-321 of SEQ ID NO: 10." Applicants submit that the this claim language is supported by the specification as filed, and does not constitute new matter.

M.P.E.P. §2163.02 states that when determining compliance with the written description requirement, "the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." M.P.E.P. §2163.02 (internal citations omitted, emphasis added). In addition, M.P.E.P. §2163.04 states that a description as filed "is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption." Therefore, "the examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." M.P.E.P. §2163.04 (internal citations omitted, emphasis added).

Paragraph [0196] of the specification states that "it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides."

Specification at paragraph [0196] (emphasis added). Figure 10 and SEQ ID NO:10 show 8 methionine residues in the sequence. Combining the statement in paragraph [0196] with the disclosure of SEQ ID NO:10, Applicants have conveyed with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicants were in possession of polypeptides of SEQ ID NO:10 beginning at any of the methionine residues listed in SEQ ID NO:10. One of the these polypeptides is the one which begins with the methionine at residue #34. Therefore, Applicants were clearly in possession of "polypeptide having the amino acid sequence of amino acids 34-321 of SEQ ID NO: 10" at the time of filing.

The PTO acknowledges that paragraph [0196] discloses that methionine residues upstream or downstream of the amino acid in position 1 may be the start amino acid. However, the PTO appears to argue that because there is more than one methionine residue in SEQ ID NO:10, Applicants have not adequately described any of the possible polypeptides of SEQ ID NO:10 beginning at a methionine residue. The PTO states that "the species methionine residue #34 as the starting amino acid is not supported by this generic disclosure because there is no express, implicit, or inherent support for this species to the exclusion of all the other species. In other words, there is no evidence that the disclosure would reasonably lead the skilled artisan to this particular species." Office Action at 15, emphasis added.

Applicants submit that this argument misstates the test for compliance with the written description requirement. The test is "whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." M.P.E.P. §2163.02 (internal citations omitted, emphasis added). Clearly, as discussed above, at the time of filing Applicants were in possession of the polypeptide of SEQ ID NO:10 starting at methionine #34 and the nucleic acid sequence which encodes this polypeptide. Contrary to the PTO's assertion, where Applicants have adequately described several polypeptides related to SEQ ID NO:10, there is nothing in the written description requirement which prevents the Applicant from claiming only one of them.

Therefore, Applicants submit that the PTO has failed to meet its initial burden of "presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims" with regard to this subject matter. M.P.E.P. §2163.04 (internal citations omitted, emphasis added). In light of

the claim amendments and arguments above, Applicants request that the PTO reconsider and withdraw the written description rejections under 35 U.S.C. §112, first paragraph.

## CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: August 8, 2005

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